

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year) 22.06.2001

Applicant's or agent's file reference
INVIT1280WO

IMPORTANT NOTIFICATION

International application No.
PCT/US00/08571

International filing date (day/month/year)
31/03/2000

Priority date (day/month/year)
31/03/1999

Applicant
INVITROGEN CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT



(PCT Article 36 and Rule 70)

Applicant's or agent's file reference INVIT1280WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/08571	International filing date (day/month/year) 31/03/2000	Priority date (day/month/year) 31/03/1999
International Patent Classification (IPC) or national classification and IPC C12N15/87		
Applicant INVITROGEN CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 12 sheets, including this cover sheet.
- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).
- These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 23/09/2000	Date of completion of this report 22.06.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Valcarcel, R Telephone No. +49 89 2399 2368 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International Application No. PCT/US00/08571

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-41 as originally filed

Claims, No.:

1-50 as originally filed

Drawings, sheets:

1/10-10/10 as originally filed

Sequence listing part of the description, pages:

1-9, filed with the letter of 07.07.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International Application No. PCT/US00/08571

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
- ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:
- ☐ the entire international application.
- ☒ claims Nos. 1-47 (with respect to industrial applicability).

because:

- ☒ the said international application, or the said claims Nos. 1-47 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separat sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International Application No. PCT/US00/08571

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .
- 2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
 - ☐ the written form has not been furnished or does not comply with the standard.
 - ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

- 1. In response to the invitation to restrict or pay additional fees the applicant has:
 - ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
- 2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
- 3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
 - ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
- 4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
 - ☒ all parts.
 - ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 7-11,19-24,29-38
	No: Claims 1-6,12-18,25-28,39-50
Inventive step (IS)	Yes: Claims NONE

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International Application No. PCT/US00/08571

	No:	Claims	1-50
Industrial applicability (IA)	Yes:	Claims	48-50
	No:	Claims	-

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item II

This communication is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document cited in the International Search Report as a P,X document would become relevant.

Re Item III

Claims 1 to 47 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

The present application lacks unity, and thus contravenes the requirements of Rule 13 PCT. There is no "special technical feature" (in the sense of Rule 13.2 PCT) which links the different methods and vectors referred to in the claims. The use of translocating peptides (e.g. VP22 or Antp) for gene transfer or protein targeting is well known (see item V of the present communication). Each combination of translocating peptides and a gene or proteins could be seen as an individual invention. However, **the IPEA has elected to carry out examination on the subject-matter of all claims.**

Re Item V

1. Reference is made to the following documents; the numbering corresponds to the order of citation in the International Search Report:

D1: INVITROGEN: 'Voyager(TM) - The power of Translocation' INVITROGEN CATALOGUE, vol. 6, no. 1, February 1999 (1999-02), page 6

D2: WO 98 32866 A (HARE PETER FRANCIS JOSEPH O ;MARIE CURIE CANCER CARE (GB); ELLIOTT) 30 July 1998 (1998-07-30)

- D3:** WO 97 05265 A (HARE PETER FRANCIS JOSEPH O ;ELLIOTT GILLIAN DAPHNE (GB)) 13 February 1997 (1997-02-13)
- D4:** ELLIOTT G ET AL: 'Intercellular trafficking of VP22 -GFP fusion proteins' GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 149-151
- D5:** MURPHY A L ET AL: 'Catch VP22: the hitch-hiker's ride to gene therapy?' GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 4-5
- D6:** WO 99 11809 A (IMP COLLEGE INNOVATIONS LTD ;CRISANTI ANDREA (GB)) 11 March 1999 (1999-03-11)
- D7:** PROCHIANTZ A: 'Getting hydrophilic compounds into cells: lessons from homeopeptides' CURRENT OPINION IN NEUROBIOLOGY,GB,LONDON, vol. 6, no. 5, 1 October 1996 (1996-10-01), pages 629-634
- D8:** PROCHIANTZ A: 'Peptide nucleic acid smugglers' NATURE BIOTECHNOLOGY,US,NATURE PUBLISHING, vol. 16, 1 September 1998 (1998-09-01), pages 819-820
- D9:** BONFANTI M ET AL: 'p21 WAF1-derived peptides linked to an internalization peptide inhibit human cancer cell growth' CANCER RESEARCH,US,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, vol. 57, 15 April 1997 (1997-04-15), pages 1442-1446
- D10:** LANGE U ET AL: 'Cell penetrating PNA constructs' JOURNAL OF NEUROCHEMISTRY,US,NEW YORK, NY, vol. 69, no. SUPPL, 20 July 1997 (1997-07-20), page S260
- D11:** WO 99 05302 A (PERKIN ELMER CORP) 4 February 1999 (1999-02-04)

2. The present application does not satisfy the criterion set forth in Article 33(2) PCT because **the subject-matter of claims 1 to 6, 12 to 18, 25, 26, 28, and 39 to 50 is not new with respect to D1.**

D1 is a section of the INVITROGEN catalogue disclosing the Voyager™ system. This system uses VP22 to translocate recombinant proteins into cells in culture. D1 discloses different methods to use the Voyager™ system to translocate proteins involved in different cellular processes. **The methods disclosed in D1 are prejudicial to the novelty of claims 1 to 6, 12 to 18, 25, 26** (a fragment of DNA bridging an ORF of a gene of interest and the sequence encoding VP22 is also a linker), **28, 39** (D1 discloses His or Myc as protein tags), **40** (any protein affecting a cellular process may be a toxic protein), **41** (for the same reason as above cited for claim 39), **42 to 47** (D1 discloses that the Voyager™ system can be used in conditions of low transfection efficiencies, it further discloses that lysates of VP22 fusion-transfected cells can be added to non-transfected cells, and the VP22 fusion will translocate to the nuclei of virtually all cells in culture; see page 1 right column, answer to the second question).

D1 further discloses vectors designed to express VP22 fusion proteins among them the vectors pVP22/Myc-His and pVP22/Myc-His. The vector pVP22/Myc-His comprises the SEQ ID NO: 1 of the present application, and the vector pVP22/Myc-His comprises SEQ ID NO: 2 of the present application. Thus, **D1 is also prejudicial to the novelty of claims 48 to 50.**

3. The teachings of D1 in combination with the standard knowledge in the art **render obvious the subject-matter of all claims which are novel over D1.** The different methods referred to in the dependent claims **do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.** Thus, the subject-matter of claims 1 to 50 does not involve an inventive step.

4. Furthermore, other documents cited in the International search Report are prejudicial to the novelty and inventive step of the claims of the present application.

D2 to D4 also disclose methods for translocating different molecules of interest by using the VP22 protein (see abstract, and claims 13 and 22 of D2). Mention is made in D3 specifically to transport of non-peptidyl molecules (see claim 7, and page 5 of the description of D3). D2 to D4 are prejudicial to the novelty of the same claims as D1 (with the exception of claims 49 and 50).

D5 is also prejudicial to the involvement of **inventive step of claims 9 and 10**. D5 specifically points out that in the VP22 system, nuclear localization of the imported fusion protein may limit its potential for treating disorders of cytoplasmic or plasma membrane origin (see page 5, left column, second paragraph). D5 further states that VP22-mediated delivery of transgene products may be useful for gene therapy if the problems with the limited delivery are solved (see page 5, left column, last paragraph). A person skilled in the art in view of this teaching would attach a nuclear export signal to the translocation polypeptide to achieve transfection into cytoplasm and nucleus of the cell in culture (as referred to in claims 9 and 10 of the present application).

Furthermore, other translocating polypeptides were known in the prior art. **D6 to D11** disclose the use of another translocating polypeptides:

- the homeodomain of antennapedia (and derivatives referred to as penetratins). This translocating polypeptide has been used to facilitate translocation of oligonucleotides, oligopeptides (e.g. see table 3 of D7), and PNAs (see D10).
- transportan (see D8 and D11).

These documents disclose fusion molecules between the molecule of interest and the translocating polypeptide. In particular, D11 refers to a methods wherein the translocating peptide and the PNA are conjugated by a disulfide bond (see claim 9).

Thus D11, is prejudicial to the novelty of claim 27 of the present application (apart of being prejudicial to the novelty of claims 1, 2, 3, and 12 to 15).

5. In summary, the combination of features which make **claims 7 to 11, 19 to 24 and 29 to 38, novel over the prior art, does not meet the requirements of the PCT in respect of inventive step** since these combinations are among straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill in order to obtain alternative (improved) translocation methods. The additional features over the prior art come within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can be readily contemplated in advance.
6. For the assessment of the present claims 1 to 47 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The EPO does not recognize as industrially applicable methods of treatment of the human body by surgery or therapy and diagnostic methods practised on the human or animal body. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
7. The present application does not meet the requirements of the PCT (see International Preliminary Examination Guidelines, Section IV, III-4.3a), because on page 41 of the description (lines 26 and 27) there are general statements which imply that the extent of the protection may be expanded in a not precisely defined way.

Re Item VI

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 99 / 24559	20 May 1999	11 November 1998	11 November 1997

Re Item VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in document D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

1. The present application does not meet the requirements of the PCT since claim 1 is not clear. Claim 1 refers to a method comprising a cell in culture with a "cell process-modifying molecule" attached to a translocating polypeptide. The expression "**cell process-modifying molecule**" is not clear. Any molecule under certain conditions can modify cell processes. Thus, the IPEA has considered that any molecule which can be attached to a translocating polypeptide falls under the scope of this claim.
2. Claim 1 is further unclear since it refers to a method comprising contacting a cell in culture under suitable conditions with a molecule attached to a translocating polypeptide. The expression "**suitable conditions**" is not clearly defined rendering the scope of the claim unclear. **Accordingly, claims 2 and 12 are also unclear** since the expression "suitable conditions" is not properly defined.
3. **Claims 48 to 50 are unclear.** Claim 48 refers to a vector comprising a polynucleotide encoding a cell process-modifying molecule **attached to a translocating polypeptide**. It is unclear from this wording if the vector comprises itself a translocating polypeptide or the polynucleotide sequence encoding it. Dependent claims 49 and 50 refer to the vector of claim 48 wherein the vector has the nucleotide sequence according to either SEQ ID No: 1 or SEQ ID NO: 2. SEQ ID NOs: 1 and 2 of the present application are **polynucleotide sequences comprising the polynucleotide sequence encoding the translocating polypeptide VP22** (see page 28, lines 15 to 28, of the present application). Thus in claims 49 and 50 the vectors do not comprise a translocating polypeptide, they comprise the **polynucleotide sequence encoding the translocating polypeptide VP22**. The

IPEA has considered for examination that claims 48 to 50 refer to vectors comprising the **polynucleotide sequence encoding a translocating polypeptide**.

4. Claim 2 refers to a method for transfecting a cell in culture with a target gene, said method comprising contacting the cell in culture **with a polynucleotide** comprising the target gene **attached to a translocating polypeptide**. It is not clear if the method of claim 2 refers to a polynucleotide molecule (comprising the target gene) attached to a translocating polypeptide, or to a polynucleotide molecule comprising the target gene attached to a **polynucleotide sequence encoding a translocating polypeptide**. The IPEA has considered that both alternatives are referred to in claim 2.
5. Claims 1 and 12 refer to methods involving the use of a molecule (or agent) **attached to a translocating polypeptide**. As stated in the previous section 4 of item VIII (see above) It is not clear if these methods refer also to a molecules attached to a **polynucleotide sequence encoding a translocating polypeptide**.

It is disclosed in page 2 of the description of the present application (last paragraph) that in the case of VP22, the cells transfected with the vector encoding the gene and the translocating polypeptide are expressing the fusion protein in the cytoplasm, and the fusion product has the ability to translocate into the nucleus of adjacent cells. Thus, the IPEA has considered that molecules attached to a **polynucleotide sequence encoding a translocating polypeptide** also fall under the scope of these claims, since once the fusion protein is initially expressed in the cytoplasm of the transfected cells, it contains a translocating polypeptide.

6. **Claim 12 is further unclear** since it refers to a method comprising contacting the cell in culture with one or more regulatory agents attached to a translocating polypeptide. The expression "**regulatory agents**" is not clear. The IPEA has considered that any molecule which can be attached to a translocating polypeptide falls under the scope of this claim.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

Gray Cary Ware & Freidenrich LLP
Attn. LEARN, June M.
4365 Executive Drive, Suite 1600
San Diego, CA 92121-2189
UNITED STATES OF AMERICA

102894-159944

Date of mailing
(day/month/year)

23/10/2000

Applicant's or agent's file reference

INVTI1280W0

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 00/08571

International filing date

(day/month/year)

31/03/2000

Applicant

INVITROGEN CORPORATION et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



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NL-2280 HV Rijswijk
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Authorized officer

Catherine Humbert

NOTES TO FORM PCT/ISA/220

These Notes are intended to give basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference INVTI1280W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 08571	International filing date (day/month/year) 31/03/2000	(Earliest) Priority Date (day/month/year) 31/03/1999
Applicant INVITROGEN CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/87 C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	INVITROGEN: "Voyager(TM) - The power of Translocation" INVITROGEN CATALOGUE, XX, XX, vol. 6, no. 1, February 1999 (1999-02), page 6 XP002140132 the whole document ---	1-50
X	WO 98 32866 A (HARE PETER FRANCIS JOSEPH O ;MARIE CURIE CANCER CARE (GB); ELLIOTT) 30 July 1998 (1998-07-30) cited in the application the whole document ---	1-48
X	WO 97 05265 A (HARE PETER FRANCIS JOSEPH O ;ELLIOTT GILLIAN DAPHNE (GB)) 13 February 1997 (1997-02-13) cited in the application the whole document ---	1-48
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 October 2000

Date of mailing of the international search report

23/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Niemann, F

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ELLIOTT G ET AL: "Intercellular trafficking of VP22 -GFP fusion proteins" GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 149-151, XP002119414 ISSN: 0969-7128 the whole document	1-48
X	MURPHY A L ET AL: "Catch VP22: the hitch-hiker's ride to gene therapy?" GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 4-5, XP002119415 ISSN: 0969-7128 the whole document	1-48
X	WO 99 11809 A (IMP COLLEGE INNOVATIONS LTD ;CRISANTI ANDREA (GB)) 11 March 1999 (1999-03-11) the whole document	1-3, 5-15, 17-48
X	PROCHIANTZ A: "Getting hydrophilic compounds into cells: lessons from homeopeptides" CURRENT OPINION IN NEUROBIOLOGY,GB,LONDON, vol. 6, no. 5, 1 October 1996 (1996-10-01), pages 629-634, XP002087113 ISSN: 0959-4388 the whole document	1-3, 5-15, 17-48
X	PROCHIANTZ A: "Peptide nucleic acid smugglers" NATURE BIOTECHNOLOGY,US,NATURE PUBLISHING, vol. 16, 1 September 1998 (1998-09-01), pages 819-820, XP002088768 ISSN: 1087-0156 the whole document	1-3, 5-15, 17-48
X	BONFANTI M ET AL: "p21 WAF1-derived peptides linked to an internalization peptide inhibit human cancer cell growth" CANCER RESEARCH,US,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, vol. 57, 15 April 1997 (1997-04-15), pages 1442-1446, XP002087115 ISSN: 0008-5472 the whole document	1-3, 5-15, 17-48

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LANGEL U ET AL: "Cell penetrating PNA constructs" JOURNAL OF NEUROCHEMISTRY,US,NEW YORK, NY, vol. 69, no. SUPPL, 20 July 1997 (1997-07-20), page S260 XP002088767 ISSN: 0022-3042 the whole document</p> <p>---</p>	1-3, 5-15, 17-48
X	<p>WO 99 05302 A (PERKIN ELMER CORP) 4 February 1999 (1999-02-04)</p> <p>the whole document</p> <p>---</p>	1-3, 5-15, 17-48
A	<p>FRITZ J D ET AL: "GENE TRANSFER INTO MAMMALIAN CELLS USING HISTONE-CONDENSED PLASMID DNA" HUMAN GENE THERAPY,XX,XX, vol. 7, 1 August 1996 (1996-08-01), pages 1395-1404, XP002058321 ISSN: 1043-0342 cited in the application the whole document</p> <p>---</p>	8
A	<p>NIIDOME TAKURO ET AL: "Binding of cationic alpha-helical peptides to plasmid DNA and their gene transfer abilities into cells." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 24, 1997, pages 15307-15312, XP002149406 ISSN: 0021-9258 cited in the application the whole document</p> <p>---</p>	8
A	<p>ZAITSEV S V ET AL: "H1 and HMG17 extracted from calf thymus nuclei are efficient DNA carriers in gene transfer." GENE THERAPY, vol. 4, no. 6, 1997, pages 586-592, XP000952517 ISSN: 0969-7128 cited in the application the whole document</p> <p>---</p>	8
A	<p>WEN W ET AL: "IDENTIFICATION OF A SIGNAL FOR RAPID EXPORT OF PROTEINS FROM THE NUCLEUS" CELL,US,CELL PRESS, CAMBRIDGE, NA, vol. 82, 11 August 1995 (1995-08-11), pages 463-473, XP002912310 ISSN: 0092-8674 cited in the application the whole document</p> <p>---</p>	9,10

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>CHEN XIAOZHUO ET AL: "A SELF-INITIATING EUKARYOTIC TRANSIENT GENE EXPRESSION SYSTEM BASED ON COTRANSFECTION OF BACTERIOPHAGE T7 TNA POLYMERASE AND DNA VECTORS CONTAINING A T7 AUTOGENE" NUCLEIC ACIDS RESEARCH,GB,OXFORD UNIVERSITY PRESS, SURREY, vol. 22, no. 11, 11 June 1994 (1994-06-11), pages 2114-2120, XP002029322 ISSN: 0305-1048 cited in the application the whole document</p>	19-22
P,X	<p>WO 99 24559 A (ACTINOVA LTD ;AXCRONA EUGEN JAN KAROL (SE); LEANDERSSON TOMAS BORJ) 20 May 1999 (1999-05-20) the whole document</p>	1-3, 5-15, 17-48

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/08571

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-48 as far as they concerns in vivo methods are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9832866	A	30-07-1998	AU 5674998 A EP 0961829 A US 6017735 A	18-08-1998 08-12-1999 25-01-2000
WO 9705265	A	13-02-1997	AU 705563 B AU 6623996 A BR 9610058 A CA 2227786 A CN 1208438 A EP 0845043 A JP 11510386 T	27-05-1999 26-02-1997 27-07-1999 13-02-1997 17-02-1999 03-06-1998 14-09-1999
WO 9911809	A	11-03-1999	AU 8877698 A EP 1009847 A	22-03-1999 21-06-2000
WO 9905302	A	04-02-1999	AU 8408098 A EP 0998577 A US 6025140 A	16-02-1999 10-05-2000 15-02-2000
WO 9924559	A	20-05-1999	AU 1045999 A EP 1036167 A	31-05-1999 20-09-2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference INVTI1280W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 08571	International filing date (day/month/year) 31/03/2000	(Earliest) Priority Date (day/month/year) 31/03/1999
Applicant INVITROGEN CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

US 00/08571

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12N15/87 C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	INVITROGEN: "Voyager(TM) - The power of Translocation" INVITROGEN CATALOGUE, XX, XX, vol. 6, no. 1, February 1999 (1999-02), page 6 XP002140132 the whole document	1-50
X	WO 98 32866 A (HARE PETER FRANCIS JOSEPH O ;MARIE CURIE CANCER CARE (GB); ELLIOTT) 30 July 1998 (1998-07-30) cited in the application the whole document	1-48
X	WO 97 05265 A (HARE PETER FRANCIS JOSEPH O ;ELLIOTT GILLIAN DAPHNE (GB)) 13 February 1997 (1997-02-13) cited in the application the whole document	1-48
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

6 October 2000

Date of mailing of the international search report

23/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Niemann, F

INTERNATIONAL SEARCH REPORT

International Application No

P US 00/08571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ELLIOTT G ET AL: "Intercellular trafficking of VP22 -GFP fusion proteins" GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 149-151, XP002119414 ISSN: 0969-7128 the whole document	1-48
X	MURPHY A L ET AL: "Catch VP22: the hitch-hiker's ride to gene therapy?" GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 4-5, XP002119415 ISSN: 0969-7128 the whole document	1-48
X	WO 99 11809 A (IMP COLLEGE INNOVATIONS LTD ;CRISANTI ANDREA (GB)) 11 March 1999 (1999-03-11) the whole document	1-3, 5-15, 17-48
X	PROCHIANTZ A: "Getting hydrophilic compounds into cells: lessons from homeopeptides" CURRENT OPINION IN NEUROBIOLOGY,GB,LONDON, vol. 6, no. 5, 1 October 1996 (1996-10-01), pages 629-634, XP002087113 ISSN: 0959-4388 the whole document	1-3, 5-15, 17-48
X	PROCHIANTZ A: "Peptide nucleic acid smugglers" NATURE BIOTECHNOLOGY,US,NATURE PUBLISHING, vol. 16, 1 September 1998 (1998-09-01), pages 819-820, XP002088768 ISSN: 1087-0156 the whole document	1-3, 5-15, 17-48
X	BONFANTI M ET AL: "p21 WAF1-derived peptides linked to an internalization peptide inhibit human cancer cell growth" CANCER RESEARCH,US,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, vol. 57, 15 April 1997 (1997-04-15), pages 1442-1446, XP002087115 ISSN: 0008-5472 the whole document	1-3, 5-15, 17-48

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INTERNATIONAL SEARCH REPORT

International Application No

US 00/08571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LANGEL U ET AL: "Cell penetrating PNA constructs" JOURNAL OF NEUROCHEMISTRY, US, NEW YORK, NY, vol. 69, no. SUPPL, 20 July 1997 (1997-07-20), page S260 XP002088767 ISSN: 0022-3042 the whole document</p> <p>---</p>	<p>1-3, 5-15, 17-48</p>
X	<p>WO 99 05302 A (PERKIN ELMER CORP) 4 February 1999 (1999-02-04)</p> <p>the whole document</p> <p>---</p>	<p>1-3, 5-15, 17-48</p>
A	<p>FRITZ J D ET AL: "GENE TRANSFER INTO MAMMALIAN CELLS USING HISTONE-CONDENSED PLASMID DNA" HUMAN GENE THERAPY, XX, XX, vol. 7, 1 August 1996 (1996-08-01), pages 1395-1404, XP002058321 ISSN: 1043-0342 cited in the application the whole document</p> <p>---</p>	<p>8</p>
A	<p>NIIDOME TAKURO ET AL: "Binding of cationic alpha-helical peptides to plasmid DNA and their gene transfer abilities into cells." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 24, 1997, pages 15307-15312, XP002149406 ISSN: 0021-9258 cited in the application the whole document</p> <p>---</p>	<p>8</p>
A	<p>ZAITSEV S V ET AL: "H1 and HMG17 extracted from calf thymus nuclei are efficient DNA carriers in gene transfer." GENE THERAPY, vol. 4, no. 6, 1997, pages 586-592, XP000952517 ISSN: 0969-7128 cited in the application the whole document</p> <p>---</p>	<p>8</p>
A	<p>WEN W ET AL: "IDENTIFICATION OF A SIGNAL FOR RAPID EXPORT OF PROTEINS FROM THE NUCLEUS" CELL, US, CELL PRESS, CAMBRIDGE, NA, vol. 82, 11 August 1995 (1995-08-11), pages 463-473, XP002912310 ISSN: 0092-8674 cited in the application the whole document</p> <p>---</p>	<p>9,10</p>

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INTERNATIONAL SEARCH REPORT

International Application No

US 00/08571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEN XIAOZHUO ET AL: "A SELF-INITIATING EUKARYOTIC TRANSIENT GENE EXPRESSION SYSTEM BASED ON COTRANSFECTION OF BACTERIOPHAGE T7 TNA POLYMERASE AND DNA VECTORS CONTAINING A T7 AUTOGENE" NUCLEIC ACIDS RESEARCH, GB, OXFORD UNIVERSITY PRESS, SURREY, vol. 22, no. 11, 11 June 1994 (1994-06-11), pages 2114-2120, XP002029322 ISSN: 0305-1048 cited in the application the whole document ---	19-22
P, X	WO 99 24559 A (ACTINOVA LTD ; AXCRONA EUGEN JAN KAROL (SE); LEANDERSSON TOMAS BORJ) 20 May 1999 (1999-05-20) the whole document -----	1-3, 5-15, 17-48

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US 00/08571

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9832866	A	30-07-1998	AU 5674998 A EP 0961829 A US 6017735 A	18-08-1998 08-12-1999 25-01-2000
WO 9705265	A	13-02-1997	AU 705563 B AU 6623996 A BR 9610058 A CA 2227786 A CN 1208438 A EP 0845043 A JP 11510386 T	27-05-1999 26-02-1997 27-07-1999 13-02-1997 17-02-1999 03-06-1998 14-09-1999
WO 9911809	A	11-03-1999	AU 8877698 A EP 1009847 A	22-03-1999 21-06-2000
WO 9905302	A	04-02-1999	AU 8408098 A EP 0998577 A US 6025140 A	16-02-1999 10-05-2000 15-02-2000
WO 9924559	A	20-05-1999	AU 1045999 A EP 1036167 A	31-05-1999 20-09-2000

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

Gray Cary Ware & Freidenrich LLP
Attn. LEARN, June M.
4365 Executive Drive, Suite 1600
San Diego, CA 92121-2189
UNITED STATES OF AMERICA

102894-159944

Date of mailing
(day/month/year)

23/10/2000

Applicant's or agent's file reference

INVTI1280W0

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/US 00/08571

International filing date
(day/month/year)

31/03/2000

Applicant

INVITROGEN CORPORATION et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Catherine Humbert

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the International application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference INVTI1280W0	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 08571	International filing date (day/month/year) 31/03/2000	(Earliest) Priority Date (day/month/year) 31/03/1999
Applicant INVITROGEN CORPORATION et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☒ furnished subsequently to this Authority in written form.

☒ furnished subsequently to this Authority in computer readable form.

☒ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☒ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of Invention is lacking** (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ **None of the figures.**

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 00/08571

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C12N15/87 C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	INVITROGEN: "Voyager(TM) - The power of Translocation" INVITROGEN CATALOGUE, XX, XX, vol. 6, no. 1, February 1999 (1999-02), page 6 XP002140132 the whole document	1-50
X	WO 98 32866 A (HARE PETER FRANCIS JOSEPH O ;MARIE CURIE CANCER CARE (GB); ELLIOTT) 30 July 1998 (1998-07-30) cited in the application the whole document	1-48
X	WO 97 05265 A (HARE PETER FRANCIS JOSEPH O ;ELLIOTT GILLIAN DAPHNE (GB)) 13 February 1997 (1997-02-13) cited in the application the whole document	1-48
	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 October 2000

Date of mailing of the international search report

23/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
 Fax: (+31-70) 340-3016

Authorized officer

Niemann, F

INTERNATIONAL SEARCH REPORT

International Application No

PCT 00/08571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ELLIOTT G ET AL: "Intercellular trafficking of VP22 -GFP fusion proteins" GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 149-151, XP002119414 ISSN: 0969-7128 the whole document	1-48
X	MURPHY A L ET AL: "Catch VP22: the hitch-hiker's ride to gene therapy?" GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 4-5, XP002119415 ISSN: 0969-7128 the whole document	1-48
X	WO 99 11809 A (IMP COLLEGE INNOVATIONS LTD ;CRISANTI ANDREA (GB)) 11 March 1999 (1999-03-11) the whole document	1-3, 5-15, 17-48
X	PROCHIANTZ A: "Getting hydrophilic compounds into cells: lessons from homeopeptides" CURRENT OPINION IN NEUROBIOLOGY,GB,LONDON, vol. 6, no. 5, 1 October 1996 (1996-10-01), pages 629-634, XP002087113 ISSN: 0959-4388 the whole document	1-3, 5-15, 17-48
X	PROCHIANTZ A: "Peptide nucleic acid smugglers" NATURE BIOTECHNOLOGY,US,NATURE PUBLISHING, vol. 16, 1 September 1998 (1998-09-01), pages 819-820, XP002088768 ISSN: 1087-0156 the whole document	1-3, 5-15, 17-48
X	BONFANTI M ET AL: "p21 WAF1-derived peptides linked to an internalization peptide inhibit human cancer cell growth" CANCER RESEARCH,US,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, vol. 57, 15 April 1997 (1997-04-15), pages 1442-1446, XP002087115 ISSN: 0008-5472 the whole document	1-3, 5-15, 17-48

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/08571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LANGEL U ET AL: "Cell penetrating PNA constructs" JOURNAL OF NEUROCHEMISTRY, US, NEW YORK, NY, vol. 69, no. SUPPL, 20 July 1997 (1997-07-20), page S260 XP002088767 ISSN: 0022-3042 the whole document</p>	1-3, 5-15, 17-48
X	<p>WO 99 05302 A (PERKIN ELMER CORP) 4 February 1999 (1999-02-04) the whole document</p>	1-3, 5-15, 17-48
A	<p>FRITZ J D ET AL: "GENE TRANSFER INTO MAMMALIAN CELLS USING HISTONE-CONDENSED PLASMID DNA" HUMAN GENE THERAPY, XX, XX, vol. 7, 1 August 1996 (1996-08-01), pages 1395-1404, XP002058321 ISSN: 1043-0342 cited in the application the whole document</p>	8
A	<p>NIIDOME TAKURO ET AL: "Binding of cationic alpha-helical peptides to plasmid DNA and their gene transfer abilities into cells." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 24, 1997, pages 15307-15312, XP002149406 ISSN: 0021-9258 cited in the application the whole document</p>	8
A	<p>ZAITSEV S V ET AL: "H1 and HMG17 extracted from calf thymus nuclei are efficient DNA carriers in gene transfer." GENE THERAPY, vol. 4, no. 6, 1997, pages 586-592, XP000952517 ISSN: 0969-7128 cited in the application the whole document</p>	8
A	<p>WEN W ET AL: "IDENTIFICATION OF A SIGNAL FOR RAPID EXPORT OF PROTEINS FROM THE NUCLEUS" CELL, US, CELL PRESS, CAMBRIDGE, NA, vol. 82, 11 August 1995 (1995-08-11), pages 463-473, XP002912310 ISSN: 0092-8674 cited in the application the whole document</p>	9, 10

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INTERNATIONAL SEARCH REPORT

International Application No

PCT 00/08571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEN XIAOZHUO ET AL: "A SELF-INITIATING EUKARYOTIC TRANSIENT GENE EXPRESSION SYSTEM BASED ON COTRANSFECTION OF BACTERIOPHAGE T7 TNA POLYMERASE AND DNA VECTORS CONTAINING A T7 AUTOGENE" NUCLEIC ACIDS RESEARCH,GB,OXFORD UNIVERSITY PRESS, SURREY, vol. 22, no. 11, 11 June 1994 (1994-06-11), pages 2114-2120, XP002029322 ISSN: 0305-1048 cited in the application the whole document	19-22
P, X	WO 99 24559 A (ACTINOVA LTD ;AXCRONA EUGEN JAN KAROL (SE); LEANDERSSON TOMAS BORJ) 20 May 1999 (1999-05-20) the whole document	1-3, 5-15, 17-48

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/08571

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-48 as far as they concerns in vivo methods are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT 00/08571

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9832866 A	30-07-1998	AU 5674998 A EP 0961829 A US 6017735 A	18-08-1998 08-12-1999 25-01-2000
WO 9705265 A	13-02-1997	AU 705563 B AU 6623996 A BR 9610058 A CA 2227786 A CN 1208438 A EP 0845043 A JP 11510386 T	27-05-1999 26-02-1997 27-07-1999 13-02-1997 17-02-1999 03-06-1998 14-09-1999
WO 9911809 A	11-03-1999	AU 8877698 A EP 1009847 A	22-03-1999 21-06-2000
WO 9905302 A	04-02-1999	AU 8408098 A EP 0998577 A US 6025140 A	16-02-1999 10-05-2000 15-02-2000
WO 9924559 A	20-05-1999	AU 1045999 A EP 1036167 A	31-05-1999 20-09-2000

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
5 October 2000 (05.10.2000)

PCT

(10) International Publication Number
WO 00/58488 A3

- (51) International Patent Classification⁷: C12N 15/87, 15/62 (74) Agent: LEARN, June, M.; Gray Cary Ware & Freidenrich LLP, Suite 1600, 4365 Executive Drive, San Diego, CA 92121 (US).
- (21) International Application Number: PCT/US00/08571 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (22) International Filing Date: 31 March 2000 (31.03.2000)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 60/127,467 31 March 1999 (31.03.1999) US (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
- (63) Related by continuation (CON) or continuation-in-part (CIP) to earlier application:
US 60/127,467 (CIP)
Filed on 31 March 1999 (31.03.1999)
- (71) Applicant (*for all designated States except US*): INVITROGEN CORPORATION [US/US]; 1600 Faraday Avenue, Carlsbad, CA 92008 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): DALBY, Brian [GB/US]; 2803 Unicornio Street, Carlsbad, CA 92009 (US). BENNETT, Robert, P. [US/US]; 1269 Rainbow Ridge Lane, Encinitas, CA 92024 (US).
- Published:
— With international search report.
- (88) Date of publication of the international search report:
18 January 2001
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: DELIVERY OF FUNCTIONAL PROTEIN SEQUENCES BY TRANSLOCATING POLYPEPTIDES

(57) Abstract: The invention provides methods for modulating a cellular process by contacting a cell in culture with a cell process-modifying molecule attached to a translocating polypeptide. For example, in one embodiment, a cell in culture is transfected with a target gene by contacting the cell in culture with a polynucleotide (that contains the target gene) attached to a translocating polypeptide. In another embodiment, expression of a target gene product in a cell in culture that contains a target gene under control of one or more regulatory elements is modulated by contacting the cell in culture with one or more regulatory agents attached to a translocating polypeptide. The one or more regulatory agents are translocated into the cell in culture and interact therein with the one or more regulatory elements to modulate expression of the target gene product by the cell.

WO 00/58488 A3

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 00/08571

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/87 C12N15/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

6 October 2000

Date of mailing of the international search report

23/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Niemann, F

INTERNATIONAL SEARCH REPORT

Intern. Publication No.

PCT/US 00/08571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ELLIOTT G ET AL: "Intercellular trafficking of VP22 -GFP fusion proteins" GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 149-151, XP002119414 ISSN: 0969-7128 the whole document ---	1-48
X	MURPHY A L ET AL: "Catch VP22: the hitch-hiker's ride to gene therapy?" GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 4-5, XP002119415 ISSN: 0969-7128 the whole document ---	1-48
X	WO 99 11809 A (IMP COLLEGE INNOVATIONS LTD ;CRISANTI ANDREA (GB)) 11 March 1999 (1999-03-11) the whole document ---	1-3, 5-15, 17-48
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X	BONFANTI M ET AL: "p21 WAF1-derived peptides linked to an internalization peptide inhibit human cancer cell growth" CANCER RESEARCH,US,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, vol. 57, 15 April 1997 (1997-04-15), pages 1442-1446, XP002087115 ISSN: 0008-5472 the whole document ---	1-3, 5-15, 17-48

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INTERNATIONAL SEARCH REPORT

Inter: Application No

PCT/US 00/08571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LANGE U ET AL: "Cell penetrating PNA constructs"</p> <p>JOURNAL OF NEUROCHEMISTRY, US, NEW YORK, NY, vol. 69, no. SUPPL, 20 July 1997 (1997-07-20), page S260</p> <p>XP002088767</p> <p>ISSN: 0022-3042</p> <p>the whole document</p> <p>---</p>	1-3, 5-15, 17-48
X	<p>WO 99 05302 A (PERKIN ELMER CORP)</p> <p>4 February 1999 (1999-02-04)</p> <p>the whole document</p> <p>---</p>	1-3, 5-15, 17-48
A	<p>FRITZ J D ET AL: "GENE TRANSFER INTO MAMMALIAN CELLS USING HISTONE-CONDENSED PLASMID DNA"</p> <p>HUMAN GENE THERAPY, XX, XX, vol. 7, 1 August 1996 (1996-08-01), pages 1395-1404, XP002058321</p> <p>ISSN: 1043-0342</p> <p>cited in the application</p> <p>the whole document</p> <p>---</p>	8
A	<p>NIIDOME TAKURO ET AL: "Binding of cationic alpha-helical peptides to plasmid DNA and their gene transfer abilities into cells."</p> <p>JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 24, 1997, pages 15307-15312, XP002149406</p> <p>ISSN: 0021-9258</p> <p>cited in the application</p> <p>the whole document</p> <p>---</p>	8
A	<p>ZAITSEV S V ET AL: "H1 and HMG17 extracted from calf thymus nuclei are efficient DNA carriers in gene transfer." GENE THERAPY, vol. 4, no. 6, 1997, pages 586-592, XP000952517</p> <p>ISSN: 0969-7128</p> <p>cited in the application</p> <p>the whole document</p> <p>---</p>	8
A	<p>WEN W ET AL: "IDENTIFICATION OF A SIGNAL FOR RAPID EXPORT OF PROTEINS FROM THE NUCLEUS"</p> <p>CELL, US, CELL PRESS, CAMBRIDGE, MA, vol. 82, 11 August 1995 (1995-08-11), pages 463-473, XP002912310</p> <p>ISSN: 0092-8674</p> <p>cited in the application</p> <p>the whole document</p> <p>---</p> <p>-/--</p>	9,10

INTERNATIONAL SEARCH REPORT

Inter Application No

PCT/US 00/08571

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	CHEN XIAOZHUO ET AL: "A SELF-INITIATING EUKARYOTIC TRANSIENT GENE EXPRESSION SYSTEM BASED ON COTRANSFECTION OF BACTERIOPHAGE T7 TNA POLYMERASE AND DNA VECTORS CONTAINING A T7 AUTOGENE" NUCLEIC ACIDS RESEARCH,GB,OXFORD UNIVERSITY PRESS, SURREY, vol. 22, no. 11, 11 June 1994 (1994-06-11), pages 2114-2120, XP002029322 ISSN: 0305-1048 cited in the application the whole document	19-22
P,X	WO 99 24559 A (ACTINOVA LTD ;AXCRONA EUGEN JAN KAROL (SE); LEANDERSSON TOMAS BORJ) 20 May 1999 (1999-05-20) the whole document	1-3, 5-15, 17-48

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter national application No

PCT/US 99/08571

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9832866	A	30-07-1998	AU 5674998 A EP 0961829 A US 6017735 A	18-08-1998 08-12-1999 25-01-2000
WO 9705265	A	13-02-1997	AU 705563 B AU 6623996 A BR 9610058 A CA 2227786 A CN 1208438 A EP 0845043 A JP 11510386 T	27-05-1999 26-02-1997 27-07-1999 13-02-1997 17-02-1999 03-06-1998 14-09-1999
WO 9911809	A	11-03-1999	AU 8877698 A EP 1009847 A	22-03-1999 21-06-2000
WO 9905302	A	04-02-1999	AU 8408098 A EP 0998577 A US 6025140 A	16-02-1999 10-05-2000 15-02-2000
WO 9924559	A	20-05-1999	AU 1045999 A EP 1036167 A	31-05-1999 20-09-2000

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 26 JUN 2001

WIPO PCT

Applicant's or agent's file reference INVIT1280WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/08571	International filing date (day/month/year) 31/03/2000	Priority date (day/month/year) 31/03/1999
International Patent Classification (IPC) or national classification and IPC C12N15/87		
Applicant INVITROGEN CORPORATION et al.		

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1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 12 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

 These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 23/09/2000	Date of completion of this report 22.06.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Valcarcel, R Telephone No. +49 89 2399 2368



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/08571

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*

Description, pages:

1-41 as originally filed

Claims, No.:

1-50 as originally filed

Drawings, sheets:

1/10-10/10 as originally filed

Sequence listing part of the description, pages:

1-9, filed with the letter of 07.07.2000

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☒ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☒ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/08571

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-47 (with respect to industrial applicability).

because:

☒ the said international application, or the said claims Nos. 1-47 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/08571

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .
- 2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
 - ☐ the written form has not been furnished or does not comply with the standard.
 - ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:
 - ☐ restricted the claims.
 - ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☐ neither restricted nor paid additional fees.
2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
 - ☐ complied with.
 - ☒ not complied with for the following reasons:
see separate sheet
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
 - ☒ all parts.
 - ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-11,19-24,29-38
	No:	Claims	1-6,12-18,25-28,39-50
Inventive step (IS)	Yes:	Claims	NONE

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	No:	Claims	1-50
Industrial applicability (IA)	Yes:	Claims	48-50
	No:	Claims	-

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

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Re Item II

This communication is based on the assumption that all claims enjoy priority rights from the filing date of the priority document. If it later turns out that this is not correct, the document cited in the International Search Report as a P,X document would become relevant.

Re Item III

Claims 1 to 47 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item IV

The present application lacks unity, and thus contravenes the requirements of Rule 13 PCT. There is no "special technical feature" (in the sense of Rule 13.2 PCT) which links the different methods and vectors referred to in the claims. The use of translocating peptides (e.g. VP22 or Antp) for gene transfer or protein targeting is well known (see item V of the present communication). Each combination of translocating peptides and a gene or proteins could be seen as an individual invention. However, **the IPEA has elected to carry out examination on the subject-matter of all claims.**

Re Item V

1. Reference is made to the following documents; the numbering corresponds to the order of citation in the International Search Report:

D1: INVITROGEN: 'Voyager(TM) - The power of Translocation' INVITROGEN CATALOGUE, vol. 6, no. 1, February 1999 (1999-02), page 6

D2: WO 98 32866 A (HARE PETER FRANCIS JOSEPH O ;MARIE CURIE CANCER CARE (GB); ELLIOTT) 30 July 1998 (1998-07-30)

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/08571

- D3:** WO 97 05265 A (HARE PETER FRANCIS JOSEPH O ;ELLIOTT GILLIAN DAPHNE (GB)) 13 February 1997 (1997-02-13)
- D4:** ELLIOTT G ET AL: 'Intercellular trafficking of VP22 -GFP fusion proteins' GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 149-151
- D5:** MURPHY A L ET AL: 'Catch VP22: the hitch-hiker's ride to gene therapy?' GENE THERAPY,GB,MACMILLAN PRESS LTD., BASINGSTOKE, vol. 6, no. 1, January 1999 (1999-01), pages 4-5
- D6:** WO 99 11809 A (IMP COLLEGE INNOVATIONS LTD ;CRISANTI ANDREA (GB)) 11 March 1999 (1999-03-11)
- D7:** PROCHIA NTZ A: 'Getting hydrophilic compounds into cells: lessons from homeopeptides' CURRENT OPINION IN NEUROBIOLOGY,GB,LONDON, vol. 6, no. 5, 1 October 1996 (1996-10-01), pages 629-634
- D8:** PROCHIA NTZ A: 'Peptide nucleic acid smugglers' NATURE BIOTECHNOLOGY,US,NATURE PUBLISHING, vol. 16, 1 September 1998 (1998-09-01), pages 819-820
- D9:** BONFANTI M ET AL: 'p21 WAF1-derived peptides linked to an internalization peptide inhibit human cancer cell growth' CANCER RESEARCH,US,AMERICAN ASSOCIATION FOR CANCER RESEARCH, BALTIMORE, MD, vol. 57, 15 April 1997 (1997-04-15), pages 1442-1446
- D10:** LANGE L U ET AL: 'Cell penetrating PNA constructs' JOURNAL OF NEUROCHEMISTRY,US,NEW YORK, NY, vol. 69, no. SUPPL, 20 July 1997 (1997-07-20), page S260
- D11:** WO 99 05302 A (PERKIN ELMER CORP) 4 February 1999 (1999-02-04)

2. The present application does not satisfy the criterion set forth in Article 33(2) PCT because **the subject-matter of claims 1 to 6, 12 to 18, 25, 26, 28, and 39 to 50 is not new with respect to D1.**

D1 is a section of the INVITROGEN catalogue disclosing the Voyager™ system. This system uses VP22 to translocate recombinant proteins into cells in culture. D1 discloses different methods to use the Voyager™ system to translocate proteins involved in different cellular processes. **The methods disclosed in D1 are prejudicial to the novelty of claims 1 to 6, 12 to 18, 25, 26** (a fragment of DNA bridging an ORF of a gene of interest and the sequence encoding VP22 is also a linker), **28, 39** (D1 discloses His or Myc as protein tags), **40** (any protein affecting a cellular process may be a toxic protein), **41** (for the same reason as above cited for claim 39), **42 to 47** (D1 discloses that the Voyager™ system can be used in conditions of low transfection efficiencies, it further discloses that lysates of VP22 fusion-transfected cells can be added to non-transfected cells, and the VP22 fusion will translocate to the nuclei of virtually all cells in culture; see page 1 right column, answer to the second question).

D1 further discloses vectors designed to express VP22 fusion proteins among them the vectors pVP22/Myc-His and pVP22/Myc-His. The vector pVP22/Myc-His comprises the SEQ ID NO: 1 of the present application, and the vector pVP22/Myc-His comprises SEQ ID NO: 2 of the present application. Thus, **D1 is also prejudicial to the novelty of claims 48 to 50.**

3. The teachings of D1 in combination with the standard knowledge in the art **render obvious the subject-matter of all claims which are novel over D1.** The different methods referred to in the dependent claims **do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.** Thus, **the subject-matter of claims 1 to 50 does not involve an inventive step.**

4. Furthermore, other documents cited in the International search Report are prejudicial to the novelty and inventive step of the claims of the present application.

D2 to D4 also disclose methods for translocating different molecules of interest by using the VP22 protein (see abstract, and claims 13 and 22 of D2). Mention is made in D3 specifically to transport of non-peptidyl molecules (see claim 7, and page 5 of the description of D3). D2 to D4 are prejudicial to the novelty of the same claims as D1 (with the exception of claims 49 and 50).

D5 is also prejudicial to the involvement of **inventive step of claims 9 and 10**. D5 specifically points out that in the VP22 system, nuclear localization of the imported fusion protein may limit its potential for treating disorders of cytoplasmic or plasma membrane origin (see page 5, left column, second paragraph). D5 further states that VP22-mediated delivery of transgene products may be useful for gene therapy if the problems with the limited delivery are solved (see page 5, left column, last paragraph). A person skilled in the art in view of this teaching would attach a nuclear export signal to the translocation polypeptide to achieve transfection into cytoplasm and nucleus of the cell in culture (as referred to in claims 9 and 10 of the present application).

Furthermore, other translocating polypeptides were known in the prior art. **D6 to D11** disclose the use of another translocating polypeptides:

- the homeodomain of antennapedia (and derivatives referred to as penetratins). This translocating polypeptide has been used to facilitate translocation of oligonucleotides, oligopeptides (e.g. see table 3 of D7), and PNAs (see D10).
- transportan (see D8 and D11).

These documents disclose fusion molecules between the molecule of interest and the translocating polypeptide. In particular, D11 refers to a methods wherein the translocating peptide and the PNA are conjugated by a disulfide bond (see claim 9).

Thus D11, is prejudicial to the novelty of claim 27 of the present application (apart of being prejudicial to the novelty of claims 1,2, 3, and 12 to 15).

**INTERNATIONAL PRELIMINARY
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International application No. PCT/US00/08571

5. In summary, the combination of features which make **claims 7 to 11, 19 to 24 and 29 to 38, novel over the prior art, does not meet the requirements of the PCT in respect of inventive step** since these combinations are among straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill in order to obtain alternative (improved) translocation methods. The additional features over the prior art come within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can be readily contemplated in advance.
6. For the assessment of the present claims 1 to 47 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The EPO does not recognize as industrially applicable methods of treatment of the human body by surgery or therapy and diagnostic methods practised on the human or animal body. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
7. The present application does not meet the requirements of the PCT (see International Preliminary Examination Guidelines, Section IV, III-4.3a), because on page 41 of the description (lines 26 and 27) there are general statements which imply that the extent of the protection may be expanded in a not precisely defined way.

Re Item VI

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO 99 / 24559	20 May 1999	11 November 1998	11 November 1997

Re Item VII

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in document D1 is not mentioned in the description, nor is this document identified therein.

Re Item VIII

1. The present application does not meet the requirements of the PCT since claim 1 is not clear. Claim 1 refers to a method comprising a cell in culture with a "cell process-modifying molecule" attached to a translocating polypeptide. The expression "**c ll process-modifying molecule**" is not clear. Any molecule under certain conditions can modify cell processes. Thus, the IPEA has considered that any molecule which can be attached to a translocating polypeptide falls under the scope of this claim.
2. Claim 1 is further unclear since it refers to a method comprising contacting a cell in culture under suitable conditions with a molecule attached to a translocating polypeptide. The expression "**suitable conditions**" is not clearly defined rendering the scope of the claim unclear. **Accordingly, claims 2 and 12 are also uncl ar** since the expression "suitable conditions" is not properly defined.
3. **Claims 48 to 50 are unclear.** Claim 48 refers to a vector comprising a polynucleotide encoding a cell process-modifying molecule **attached to a translocating polypeptide**. It is unclear from this wording if the vector comprises itself a translocating polypeptide or the polynucleotide sequence encoding it. Dependent claims 49 and 50 refer to the vector of claim 48 wherein the vector has the nucleotide sequence according to either SEQ ID No: 1 or SEQ ID NO: 2. SEQ ID NOs: 1 and 2 of the present application are **polynucleotide sequences** comprising **th polynucleotide sequence encoding the translocating polypeptide VP22** (see page 28, lines 15 to 28, of the present application). Thus in claims 49 and 50 the vectors do not comprise a translocating polypeptide, they comprise the **polynucl otid s qu nc ncoding th translocating polypeptid VP22**. The

IPEA has considered for examination that claims 48 to 50 refer to vectors comprising **the polynucleotide sequence encoding a translocating polypeptide.**

4. Claim 2 refers to a method for transfecting a cell in culture with a target gene, said method comprising contacting the cell in culture **with a polynucleotide** comprising the target gene **attached to a translocating polypeptide.** It is not clear if the method of claim 2 refers to a polynucleotide molecule (comprising the target gene) attached to a translocating polypeptide, or to a polynucleotide molecule comprising the target gene attached to a **polynucleotide sequence encoding a translocating polypeptide.** The IPEA has considered that both alternatives are referred to in claim 2.
5. Claims 1 and 12 refer to methods involving the use of a molecule (or agent) **attached to a translocating polypeptide.** As stated in the previous section 4 of item VIII (see above) It is not clear if these methods refer also to a molecules attached to a **polynucleotide sequence encoding a translocating polypeptide.**

It is disclosed in page 2 of the description of the present application (last paragraph) that in the case of VP22, the cells transfected with the vector encoding the gene and the translocating polypeptide are expressing the fusion protein in the cytoplasm, and the fusion product has the ability to translocate into the nucleus of adjacent cells. Thus, the IPEA has considered that molecules attached to a **polynucleotide sequence encoding a translocating polypeptide** also fall under the scope of these claims, since once the fusion protein is initially expressed in the cytoplasm of the transfected cells, it contains a translocating polypeptide.

6. **Claim 12 is further unclear** since it refers to a method comprising contacting the cell in culture with one or more regulatory agents attached to a translocating polypeptide. The expression "**regulatory agents**" is not clear. The IPEA has considered that any molecule which can be attached to a translocating polypeptide falls under the scope of this claim.